77. (New) A method of preparing a neural progenitor cell or a differentiated progeny thereof for storage, comprising obtaining the cell in a method according to Claim 66 and freezing the cell in the presence of a cryoprotectant.

78. (New) A method of generating purified neurons, comprising obtaining a culture purified in respect of neural progenitors, using the method of Claim 66 wherein the selectable marker is differentially expressed in neural progenitor cells and culturing the progenitors obtained in the presence of medium suitable for differentiation of the progenitor into neurons.

REMARKS

Applicants thank the Examiner for the courtesy extended to Applicants' representatives in an interview held on February 25, 2003. Upon entry of this Amendment, Claims 42, 44-51, 54, 58, and 64-78 are pending in this application. Applicants have amended the claims to more clearly reflect the intended subject matter. Support for the amendments can be found in the specification and claims as filed.

New Claims 66-75, 77, and 78 correspond to Claims 42, 44-51, 58, 64, and 65 wherein expression of the selectable marker is operatively linked to a gene that is differentially expressed in neural progenitor cells rather than to a Sox gene. Claim 76 depends from Claim 66 and specifies a number of neural progenitor cell-specific genes. Support for this claim can be found in the specification at page 12, lines 7-12; page 13, lines 3-7; page 17, lines 11-14; and page 19, lines 8-12, 23-24, and 27-29. None of the foregoing amendments introduces new matter.

Claims 42, 44-51, 54, 58, 64, and 65 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

The Examiner contends that the term "pluripotential cell" is vague and that "it is unclear as to the metes and bounds of what would be considered 'pluripotential cell.'" In an effort to render the claims more clear, and without acquiescing in the propriety of the rejection, applicants have amended claims 42, 44-49 to recite "pluripotent cells" in place of "pluripotential cells."

Applicants have amended the phrase "genetically modifying pluripotential cells to delete, mutate, substitute or add genes" in claim 45 to recite "genetically modifying pluripotent cells by deleting, mutating, substituting, or adding genes to said pluripotent cells" in order to render the phrase more clear. Applicants have also amended claim 45 and 65 to replace "neural progenitor" with "neural progenitor cells" and in claim 45 to replace "and/or" with "or . . . or both" as suggested by the Examiner. In addition, Applicants have amended claim 49 to indicate that the phrase "the method comprises forming an embroid body" modifies step (ii) of independent claim 42.

Applicants believe that the amended claims are sufficiently definite and request that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 112, second paragraph.

Claims 42, 44-51, 54, 58, 64, and 65 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification. Applicants traverse.

The Examiner contends that there is no evidence of record that using cells with a gene other than Sox 2 would produce purified neural progenitor cells. Applicants have amended these claims to specify that the selectable marker is operatively linked to a Sox gene. Based on the information provided in the specification, including a working example in which expression of the selectable marker is operatively linked to Sox 2 expression and examples showing that Sox 1 and Sox 2 are both specifically expressed

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

in neural cells, one of skill in the art would reasonably expect other Sox genes to function in a manner similar to Sox 2 in the claimed methods.

With respect to new Claims 66-78, which specify that the selectable marker is operatively linked to a gene that is differentially expressed in neural progenitor cells, Applicants submit that these claims are also enabled by the specification. The Examiner contends that the skilled person would not know how to produce purified neural progenitor cells by simply introducing a selectable marker into the cells, as it would be necessary to apply a selection pressure to remove non-neural progenitor cells. Because Claim 66-78 specify that expression of the selectable marker is operatively linked to expression of a neural progenitor cell-specific gene, the Examiner's concern is obviated. The skilled artisan would understand how to use the claimed method to obtain purified neural progenitor cells.

Moreover, many genes with expression patterns specific to neural progenitor cells were known at the filing date of the present application. In addition to the genes listed in Claim 76, which are all specifically identified in the specification, a number of other suitable genes were known. These include Gli I (see Lee *et al.*, page 2548, first paragraph of discussion), Xsna, Xslu, and XANF (Morgan & Sargent, abstract - this paper also mentions Pax 3), En-2, Krox 20, NCAM, nrp-1, otx 2, and Hox B9 (Lamb & Harland, paragraph bridging pages 3628 and 3629), Zic-r1 (Mizuseki *et al.*, see abstract), Phox 2a and Phox 2b (see Pattyn *et al.*, abstract; Morin *et al.*, abstract and page 411, right hand column paragraph 3), and GFAP (Blass-Kampmann *et al.*, abstract). Copies of these references will be forwarded to the Examiner under separate cover.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

The Examiner also contends that the specification does not enable the use of a stimulant other than retinoic acid to stimulate differentiation of pluripotent cells to neural progenitor cells. Applicants respectfully submit that the selection of a stimulant is not a critical feature of the claimed invention and that any stimulant that induces differentiation of plurpotent cells to neural cells can be used in the methods of the invention. Applicants have taught how to use the invention by providing a working example. Nothing more is necessary to enable the claimed methods.

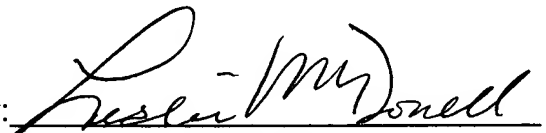
Applicants respectfully submit that the claims are now in condition for allowance and request a timely issuance of a notice of allowance.

Applicants believe that any extension of time necessary for entry of this Amendment and Response is accounted for by the accompanying Petition for Extension of Time. However, in the event of an error, please grant any additional extensions of time required to enter this Amendment and Response and charge any additional fees required to deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: May 12, 2003

By: 

Leslie A. McDonell
Reg. No. 34,872

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

APPENDIX TO AMENDMENT OF MAY 12, 2003
VERSION WITH MARKINGS TO SHOW CHANGES MADE

42. (Twice Amended) A method for generating a culture that is purified or enriched in neural progenitor cells, comprising:

(i) introducing into a pluripotent [pluripotential] cell a selectable marker that is differentially expressed in neural progenitor cells compared with its expression in other cells, wherein neural progenitor cells constitute a sub-set of the cells obtainable from the pluripotent [pluripotential] cell, and wherein expression of the selectable marker is operatively linked to expression of a Sox gene;

(ii) culturing the pluripotent [pluripotential] cell *in vitro* to induce differentiation of the pluripotent [pluripotential] cell into a neural progenitor cell or into a mixture of cells including neural progenitor cells, or to induce preferential survival, in a mixed culture of cells, of neural progenitor cells; and

(iii) selecting for neural progenitor cells according to differential expression of the selectable marker introduced in step (i).

44. (Twice Amended) A method according to Claim 42 wherein the pluripotent [pluripotential] cell is selected from embryonic stem (ES) cells, embryonic germ (EG) cells, embryonic carcinoma (EC) cells, a primary culture of fetal cells, a primary culture of post-natal cells, and a primary culture of adult cells.

45. (Twice Amended) A method according to Claim 42 comprising genetically modifying pluripotent [pluripotential] cells by deleting, mutating, substituting or adding genes in said pluripotent cells [to delete, mutate, substitute or add genes] in order (i) to

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

assay gene function in neural progenitor cells, or [, and/or] (ii) to render selected cells more suitable for transplantation, or both.

46. (Twice Amended) A method according to Claim 42 further comprising:

(iv) introducing into the pluripotent [pluripotential] cell a second selectable marker that is differentially expressed in cells of a selected sub-lineage compared with its expression in other cells, wherein cells of the selected sub-lineage are formed by differentiation of neural progenitor cells; and

(v) when a culture of neural progenitor cells has been obtained, allowing or inducing differentiation of the cells and selecting for cells that express the second selectable marker.

47. (Three Times Amended) A method according to Claim 42 wherein the selectable marker is introduced into the pluripotent [pluripotential] cell by targeted integration or random gene trap integration so as to be operatively coupled to a gene that is differentially expressed in neural progenitor cells.

48. (Three Times Amended) A method according to Claim 42 wherein the selectable marker is introduced into the pluripotent [pluripotential] cell via random integration of a transgene in which the selectable marker is operatively coupled to a gene that is differentially expressed in neural progenitor cells.

49. (Three Times Amended) A method according to Claim 42 wherein the pluripotent [pluripotential] cell is an ES, EG or EC cell and the method comprises forming an embryoid body in step (ii), or otherwise inducing differentiation of the cells.

50. A method according to Claim 49 wherein the differentiated cells are dissociated so as to form a culture comprising of individual cells.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

51. A method according to Claim 49 wherein differentiated cells of an embryoid body are dissociated using a protease, such as trypsin.

[53. (Cancelled) A method according to Claim 42 wherein the selectable marker is expressed in cells that express a Sox gene.]

54. (Amended) A method according to Claim 42 [53] wherein the Sox gene is selected from Sox 1, Sox 2 and Sox 3.

58. A method according to Claim 42 wherein the selectable marker is an antibiotic resistance gene and the method comprises culture in the presence of antibiotic.

64. A method of preparing a neural progenitor cell or a differentiated progeny thereof for storage, comprising obtaining the cell in a method according to Claim 42 and freezing the cell in the presence of a cryoprotectant.

65. (Amended) A method of generating purified neuron cells [neurons], comprising obtaining a culture [purified in respect] of neural progenitor cells [progenitors,] using the method of Claim 42 wherein the selectable marker is differentially expressed in cells that express a Sox gene, and culturing the progenitor cells [progenitors] obtained in the presence of medium suitable for differentiation of the progenitor cells into neuron cells [neurons].

66. (New) A method for generating a culture that is purified or enriched in neural progenitor cells, comprising:

(i) introducing into a pluripotent cell a selectable marker that is differentially expressed in neural progenitor cells compared with its expression in other cells, wherein neural progenitor cells constitute a sub-set of the cells obtainable from the pluripotent cell, and wherein expression of the selectable marker is operatively linked to expression

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

of a gene that is differentially expressed in neural progenitor cells,

(ii) culturing the pluripotent cell *in vitro* to induce differentiation of the pluripotent cell into a neural progenitor cell or into a mixture of cells including neural progenitor cells, or to induce preferential survival, in a mixed culture of cells, of neural progenitor cells; and

(iii) selecting for neural progenitor cells according to differential expression of the selectable marker introduced in step (i).

67. (New) A method according to Claim 66 wherein the pluripotent cell is selected from embryonic stem (ES) cells, embryonic germ (EG) cells, embryonic carcinoma (EC) cells, a primary culture of fetal cells, a primary culture of post-natal cells, and a primary culture of adult cells.

68. (New) A method according to Claim 66 comprising genetically modifying pluripotent cells by deleting, mutating, substituting, or adding genes in said pluripotent cells in order to assay gene function in neural progenitor cells, or render selected cells more suitable for transplantation, or both.

69. (New) A method according to Claim 66 further comprising:

(1) introducing into the pluripotent cell a second selectable marker that is differentially expressed in cells of a selectable sub-lineage compared with its expression in other cells, wherein cells of the selected sub-lineage are formed by differentiation of neural progenitor cells; and

(2) when a culture of neural progenitor cells has been obtained, allowing or inducing differentiation of the cells and selecting for cells that express the second selectable marker.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

70. (New) A method according to Claim 66 wherein the selectable marker is introduced into the pluripotent cell by targeted integration or random gene trap integration so as to be operatively coupled to a gene that is differentially expressed in neural progenitor cells.

71. (New) A method according to Claim 66 wherein the selectable marker is introduced into the pluripotent cell via random integration of a transgene in which the selectable marker is operatively coupled to a gene that is differentially expressed in neural progenitor cells.

72. (New) A method according to Claim 66 wherein the pluripotent cell is an ES, EG, or EC cell and the method comprises forming an embryoid body in step (ii), or otherwise inducing differentiation of the cells.

73. (New) A method according to Claim 72 wherein the differentiated cells are dissociated so as to form a culture substantially of individual cells.

74. (New) A method according to Claim 72 wherein differentiated cells of an embryoid body are dissociated using a protease, such as trypsin.

75. (New) A method according to Claim 66 wherein the selectable marker is an antibiotic resistance gene and the method comprises culture in the presence of antibiotic.

76. (New) A method according to Claim 66 wherein expression of the selectable marker is operatively linked to expression of a gene selected from the group consisting of Pax 3, delta-1, Mash-1, Math-4a, Pax 6, β3-tubulin, synapsin-1, MAP2/tau, GFAP, GABA, and islet -1/2.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

77. (New) A method of preparing a neural progenitor cell or a differentiated progeny thereof for storage, comprising obtaining the cell in a method according to Claim 66 and freezing the cell in the presence of a cryoprotectant.

78. (New) A method of generating purified neurons, comprising obtaining a culture purified in respect of neural progenitors, using the method of Claim 66 wherein the selectable marker is differentially expressed in neural progenitor cells and culturing the progenitors obtained in the presence of medium suitable for differentiation of the progenitor into neurons.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com